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Antihypertensive agents acting on the renin–angiotensin system and the risk of sepsis

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Use of antihypertensive drugs is not typically considered to be a risk factor for sepsis, although the POISE trial suggested that patients using beta-blockers had a higher incidence of adverse septic or infectious events.
- As sepsis is often associated with hypotension, more severe hypotension could occur in patients using antihypertensive drugs when infected.
- A potential safety concern of sepsis risk was raised with the angiotensin receptor blocker telmisartan.

WHAT THIS STUDY ADDS

- Angiotensin receptor blocker use in hypertensive patients is not associated with an increased risk of sepsis compared with other classes of agents used to treat hypertension.
- Angiotensin receptor blocker use was also not associated with an increased risk of renal failure or death during a septic episode.
- Angiotensin-converting enzyme inhibitor users may be at increased risk of sepsis and sepsis-related outcomes.

AIMS

In response to safety concerns from two large randomized controlled trials, we investigated whether the use of telmisartan, an angiotensin receptor blocker (ARB), ARBs as a class and angiotensin-converting enzyme inhibitors (ACEIs) increase the risk of sepsis, sepsis-associated mortality and renal failure in hypertensive patients.

METHODS

We performed a nested case–control study from a retrospective cohort of adults with hypertension from the UK General Practice Research Database diagnosed between 1 January 2000 and 30 June 2009. All subjects hospitalized with sepsis during follow-up were matched for age, sex, practice and duration of follow-up with 10 control subjects. Exposure was defined as current use of antihypertensive drugs.

RESULTS

From the cohort of 550 436 hypertensive patients, 1965 were hospitalized with sepsis during follow-up (rate 6.9 per 10 000 per year), of whom 824 died and 346 developed acute renal failure within 30 days. Compared with use of β-blockers, calcium-channel blockers or diuretics, use of ARBs, including telmisartan, was not associated with an elevated risk of sepsis (relative risk 1.09; 95% confidence interval 0.83–1.43); but use ACEIs was (relative risk 1.65; 95% confidence interval 1.42–1.93). Users of ARBs, β-blockers, calcium-channel blockers or diuretics, but not users of ACEIs, had lower rates of hospitalization for sepsis compared with untreated hypertensive patients. Findings were similar for sepsis-related 30 day mortality and renal failure.

CONCLUSIONS

Hypertensive patients treated with ARBs, including telmisartan, do not appear to be at increased risk of sepsis or sepsis-related 30 day mortality or renal failure. On the contrary, users of ACEIs may have an increased risk.

Introduction

In the context of routine review of safety data by the marketing authorization holder (Boehringer-Ingelheim International GmbH) from two large cardiovascular outcome trials (TRANSCEND and PRoFESS) [1, 2], the possibility of an increased risk of sepsis-related adverse event associated with telmisartan was raised. In the TRANSCEND trial, the rate ratio of sepsis was 1.48 [95% confidence interval (CI) 0.80–2.73], while in the PRoFESS trial it was 1.43 (95% CI 1.00–2.06) [3].

Previously, the only drugs consistently reported to be associated with an increased risk of sepsis have included immunosuppressive agents, corticosteroids and chemotherapeutic agents; antihypertensive agents were not considered to increase this risk. However, in view of the signal from the safety data referred to above, and data from POISE where death from sepsis or infection was significantly more common in patients who received metoprolol [4], it is possible that antihypertensives may increase the risk of sepsis.

Mechanistically, drugs commonly used to treat hypertension could potentially impede the activation of compensatory physiological cardiovascular responses to sepsis-induced vasodilatation. Therefore, prior treatment with antihypertensive drugs could thus give rise to more severe and sustained hypotensive episodes during sepsis, which could increase morbidity and mortality. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) inhibit the synthesis of angiotensin II (ACEIs) or block its effects (ARBs); this causes vasodilatation, and can decrease the glomerular filtration rate (GFR) because angiotensin II plays a critical role in the maintenance of GFR, especially during hypovolaemia or hypotension. Experimental models suggest a deleterious role of angiotensin II in sepsis [5, 6], but conflicting data exist with regard to whether blockade of angiotensin II improves survival in animal studies [7, 8]. A clinical study of patients hospitalized with sepsis reported that prior use of ARBs was, in fact, associated with improved survival [9]. Thus, it remains unclear whether medications that affect the synthesis or effect of angiotensin II, including ARBs and ACEIs (and, in particular, telmisartan), are associated with an increased risk of sepsis or sepsis-related adverse outcomes.

We conducted a population-based cohort study in patients with hypertension to evaluate whether the use of telmisartan, ARBs as a class and ACEIs increases the risk of sepsis and 30 day mortality and acute renal failure.

Methods

Study design

We used a population-based cohort design, with a nested case–control analysis, conducted using the UK General Practice Research Database (GPRD), to address these questions.

Data source

Data were obtained from the UK GPRD, one of the world's largest computerized databases of longitudinal primary care medical records linked with hospitalization data. It includes computerized medical records of >3.6 million active patients, with 39 million person-years of research-quality data, collected from over 350 general practices in the UK. The information recorded includes the patient's demographic characteristics, symptoms, history, medical diagnoses and drug prescriptions, as well as details of referrals to specialists and hospitals. The completeness and validity of the recorded information on diagnoses and drug exposures in the GPRD have been shown in several studies [10–12]. The GPRD has recently been linked with the Hospital Episode Statistics (HES), which records information on all hospitalizations, including data on length of stay and ward types, as well as extensive disease and procedure coding. This database has also been used for research previously [13, 14].

Study cohort

The study population included all subjects registered with an up-to-standard practice in the GPRD who were over the age of 18 years between 1 January 2000 and 30 June 2009. All subjects also had at least 2 years of observation time in the practice, defined as starting from the later of the date the subject joined the practice and the date the practice became up to standard. From this population, we identified the cohort of all subjects who had a diagnosis of, or treatment for, hypertension during the study period. The cohort was then divided into two cohorts, according to whether or not the subject belonged to regions or practices that permitted linkage with the HES hospitalization data. Only the cohort of patients with linkage with the HES hospitalization data was used as the study cohort.

The patients in this study cohort were followed, after the minimal 2 year observation time, from the earliest date of the diagnosis of, or treatment for, hypertension (cohort entry) until a diagnosis of sepsis (see case definition below), death, date of leaving the GP practice or 30 June 2009. The cohort included both prevalent and incident hypertensive patients at cohort entry. Cohort members with a history of sepsis in the 2 year baseline period prior to cohort entry were excluded (using the same diagnostic code definitions as for the case definition). Owing to the highly variable time-dependent nature of exposure to antihypertensive medication use, we used a nested case–control approach to data analysis.

Cases

The identification of the cases of sepsis occurring during follow-up was based on the HES database to identify all patients in the study cohort who were hospitalized during

the observation period with a primary hospital admission diagnosis of sepsis, defined using International Classification of Diseases (ICD-10) codes. Although codes for septicaemia were used, these definitions have been used previously in administrative database studies of sepsis [15–17], and had a positive predictive value of 89% and a negative predictive value of 80% [15]. In the more recent versions of ICD-10, the nomenclature in these codes has changed from septicaemia to sepsis [18]. Sepsis-associated mortality and renal failure were defined as death or renal failure occurring within 30 days of the admission for sepsis. The date of admission was designated as the index date.

Controls

For each case, 10 control subjects were selected from the cohort. The controls were selected from each case's risk set, that is, they also had to be active in the practice on the index date of their matched case. In addition, to control for geographical variations and secular trends in medical practice, controls were matched for age, sex, prevalent/incident status at cohort entry and general practice attended by the case. The index date for the case was taken as the index date for the matched controls.

Drug exposures

All prescriptions for ARBs, ACEIs, β-blockers, thiazide diuretics and calcium channel blockers (CCBs) written prior to the index date were identified for cases and controls. In addition, prescriptions for other antihypertensive drug classes not under study, namely α-blockers, clonidine and hydralazine, were also identified. Current use of a drug at the time of the index date was defined as a prescription given in the 90 day period prior to the index date.

Covariates

To control for potential confounding, several covariates were identified for baseline periods prior to cohort entry. Co-morbidity, including diabetes, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, cancer, human immunodeficiency virus infection, chronic liver disease, peripheral vascular disease and autoimmune diseases, was measured at any time prior to cohort entry but after the practice's up-to-standard date. The most recent measure of use of alcohol, smoking status and body mass index prior to diagnosis was also identified. Medications that may be associated with sepsis risk identified in the year prior to cohort entry included proton-pump inhibitors, nonsteroidal anti-inflammatory drugs, aspirin, statins, corticosteroids, other immunosuppressive agents and antineoplastic agents.

The severity of hypertension, based on the most recent values prior to cohort entry, was measured in different ways to control for confounding. First, systolic and diastolic blood pressure values were used as continuous variables. Second, hypertension based on these blood pressure values was classified hierarchically according to the 2007 European hypertension guidelines (ESH-ECS) guidelines by grade [19], as follows: grade 1 systolic 140–159 mmHg and/or diastolic 90–99 mmHg; grade 2, systolic 160–179 mmHg and/or diastolic 100–109 mmHg; grade 3, systolic ≥180 mmHg and/or diastolic ≥110 mmHg; and and grade 4, systolic ≥140 mmHg and diastolic <90 mmHg (isolated systolic hypertension). Patients in multiple categories were classified into their most severe category. For example, a patient with a systolic blood pressure of 165 mmHg (grade 2) and a diastolic blood pressure of 95 mmHg (grade 1) would be classified as grade 2. These blood pressure measurements have been validated indirectly in the GPRD by replicating the effects of various drugs known to affect blood pressure [20].

Data analysis

Conditional logistic regression was used to compute the crude and adjusted odds ratio of sepsis and of death associated with the current use of ARBs and ACEIs, after adjustment for the effects of the potential confounders. In view of the risk-set control selection for the nested case–control analysis, this odds ratio provides an accurate estimator of the incidence rate ratio of sepsis. The primary reference group included the use of β-blockers, CCBs or diuretics.

Several sensitivity analyses were performed to assess the robustness of the findings. Severity of hypertension was defined in three different ways, and current antihypertensive exposure was measured using varying time windows. We also performed sensitivity analyses excluding three diagnostic categories (congestive heart failure, diabetes and renal failure) to try to reduce the possibility of confounding by indication, because the study drugs are also used to treat these conditions, and these patients are more likely to develop renal failure and death during hospitalizations. Data analysis was performed with SAS version 9.1 (SAS Institute, Cary, NC, USA).

The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for the UK Medicines and Healthcare Products Regulatory Agency and the Ethics Committee of the Jewish General Hospital, Montreal.

Results

There were 1 129 062 subjects with hypertension or treated with antihypertensive drugs during the period January 2000 to June 2009 who met the inclusion criteria. As shown in Figure 1, linkage to the HES database was possible in approximately half of the cohort, namely close to 550 000 subjects; 442 patients with sepsis prior to cohort entry were excluded. In this cohort, we identified 2007 patients with a hospitalization with sepsis coded as the primary admission diagnosis in the HES database, from which 42 patients already on dialysis or had end-stage renal disease were excluded, leaving 1965 cases of sepsis (rate 6.9 per 10 000 per year). The majority of cases had

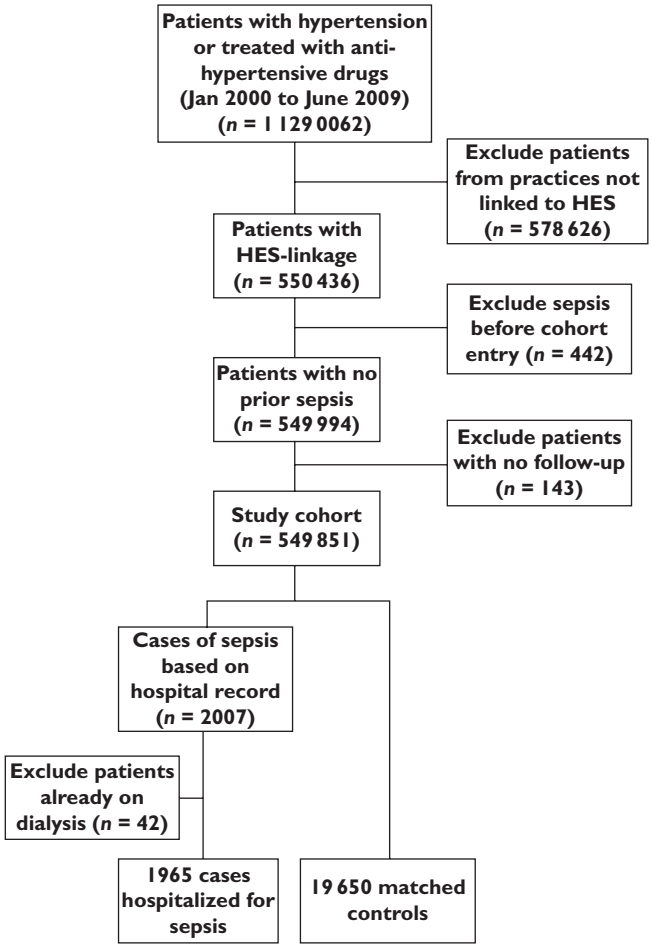

Figure 1

Flowchart describing the selection of the cases of sepsis and their matched controls from the cohort of 1 129 062 patients with hypertension or treated with antihypertensive drugs from January 2000 to June 2009, identified from the United Kingdom's General Practice Research Database (GPRD)

septicaemia (99%), of which unspecified septicaemia (ICD-10 41.9) accounted for most (67%), followed by Gram-negative septicaemia (ICD-10 41.5; 14%). The median duration of hospitalization was 9.0 days (range 4–21 day), and 346 subjects (17.6%) developed acute renal failure while 824 subjects (41.9%) died within 30 days of the admission date. The 30 day mortality of 41.9% is consistent with published rates of mortality from sepsis [21–23].

The cases were hospitalized with sepsis at a mean age of 76.6 ± 12.1 years, and 46.4% were male, identical to the matched controls at the index date (Table 1). The mean systolic blood pressure of the cases prior to cohort entry was 149.5 ± 26.7 mmHg, and 6.0% had hypertension categorized as grade 3. As expected, cases had significantly more co-morbidity, in particular diabetes, cancer, congestive heart failure, renal dysfunction, liver disease and immune disorders.

Table 1

Characteristics of cases of hospitalized sepsis and their matched controls identified from the cohort of 549 809 hypertensive patients with linkage to hospitalization data

Characteristic	Cases	Controls
Number of subjects	1965	19 650
Age at index date (years; mean ± SD)	76.6 ± 12.1	76.0 ± 11.4
Male sex (%)	52.5	52.5
Time to event or index date (years; mean ± SD)	4.1 ± 2.6	4.1 ± 2.6
Prevalent hypertension at cohort entry (%)	67.7	67.7
Diastolic blood pressure (mmHg)	85.1 ± 15.1	86.2 ± 13.7
Systolic blood pressure (mmHg)	149.5 ± 26.7	151.0 ± 25.4
Severity of hypertension (%)		
Systolic ≥180 mmHg and/or diastolic ≥110 mmHg	6.0	5.9
Systolic 160–179 mmHg and/or diastolic 100–109 mmHg	16.7	19.1
Systolic 140–159 mmHg and/or diastolic 90–99 mmHg	50.2	51.0
Other systolic and diastolic	27.1	24.0
Body mass index ≥30 kg m^{-2} (%)*	22.1	18.4
Ever smoking (%)*	29.3	27.1
Alcohol abuse (%)	7.1	4.6
Co-morbidity prior to cohort entry (%)		
Ischaemic heart disease	26.3	23.4
Diabetes	17.1	7.7
Chronic obstructive pulmonary disease	9.9	6.5
Cancer *in situ*	0.5	0.7
Solid tumour	11.9	9.0
Haematological cancer	1.6	0.4
Chronic kidney disease	4.1	1.6
Congestive heart failure	11.8	5.6
Immune disorder	5.4	2.5
Vascular disease	7.9	5.0
Liver disease	13.9	9.0
Acquired immunodeficiency sydrome	0.0	0.0
Medication use in year prior to cohort entry (%)		
Proton-pump inhibitors	15.9	12.1
Nonsteroidal anti-inflammatory drugs	23.9	22.2
Aspirin	30.8	28.1
Statins	13.5	14.4
Immunosuppressants	2.7	0.9
Chemotherapy	0.3	0.1
Corticosteroids	10.8	5.1

*Percentages among subjects with no missing data in these variables.

Table 2 shows that, compared with use of β-blockers, CCBs or diuretics, the rate of sepsis was not increased with the use of ARBs in general [relative risk (RR) 1.09; 95% CI 0.83–1.43]. The risk was also not elevated with telmisartan in particular (RR 0.60; 95% CI 0.24–1.50), although there were relatively few patients exposed to telmisartan, so that the remaining analyses focused on ARBs as a class. Use of ACEI, on the contrary, was associated with an increased rate of sepsis (RR 1.65; 95% CI 1.42–1.93). Table 2 also shows that, compared with non-users of antihypertensive

Table 2

Crude and adjusted odds ratios of hospitalized sepsis associated with current use† of ARBs and ACEIs relative to current use† of β-blockers, CCBs or diuretics (model 1) and to no antihypertensive drug use (model 2)

	Cases	Controls	Crude Odds ratio	Adjusted* Odds ratio	95% CI
Number of subjects	1965	19 650			
Model 1: comparison with other antihypertensive drugs					
Current β-blocker, CCB or diuretic use (%)	27.2	37.3	1.00	1.00	Reference
Current ARB use only (%)	3.7	3.8	1.35	1.09	0.83–1.43
Current ACEI use only (%)	17.8	12.3	2.05	1.65	1.42–1.93
Model 2: comparison with non-users of antihypertensive drugs					
No antihypertensive drug use in past year (%)	15.0	12.0	1.00	1.00	Reference
Current ARB use only (%)	3.7	3.4	0.51	0.46	0.28–0.76
Current ACEI use only (%)	17.8	12.3	1.33	1.25	0.95–1.65
Current β-blocker, CCB or diuretic use (%)	27.2	37.3	0.51	0.57	0.44–0.74

Abbreviations are as follows: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval. *Adjusted for all covariates in Table 1. †Current use refers to a prescription within 90 days prior to the index date.

Table 3

Crude and adjusted odds ratios of sepsis-related acute kidney injury or death associated with current use† of ARBs and ACEIs relative to current use† of β-blockers, CCBs or diuretics (model 1) and to no antihypertensive drug use (model 2)

	Cases	Controls	Crude Odds ratio	Adjusted* Odds ratio	95% CI
Number of subjects	993	9930			
Model 1: comparison with other antihypertensive drugs					
Current β-blocker, CCB or diuretic use (%)	27.7	38.2	1.00	1.00	Reference
Current ARB use only (%)	3.1	3.8	1.14	0.91	0.61–1.37
Current ACEI use only (%)	19.9	11.9	2.39	1.93	1.56–2.40
Model 2: comparison with non-users of antihypertensive drugs					
No antihypertensive drug use in past year (%)	13.7	11.7	1.00	1.00	Reference
Current ARB use only (%)	3.1	3.8	0.68	0.59	0.39–0.92
Current ACEI use only (%)	19.9	11.9	1.41	1.25	0.97–1.62
Current β-blocker, CCB or diuretic use (%)	27.7	38.2	0.59	0.65	0.51–0.82

Abbreviations are as for Table 1. *Adjusted for all covariates in Table 1. †Current use refers to a prescription within 90 days prior to the index date.

drugs during the year prior to the index date, ARB users (RR 0.66; 95% CI 0.50–0.88) and β-blocker, CCB or diuretic users (RR 0.60; 95% CI 0.51–0.71) appeared to have lower rates of hospitalization for sepsis. This decreased rate of sepsis was not observed for the current users of ACEIs (RR 1.00; 95% CI 0.83–1.20).

Table 3 shows that the 30 day sepsis-associated mortality was not increased with current use of ARBs (RR 0.81; 95% CI 0.50–1.30), but was increased with current use of ACEIs (RR 2.20; 95% CI 1.74–2.79), when compared with users of the other drug classes. In Table 4, 17.6% of sepsis cases (346 patients) were diagnosed with acute renal failure in the 30 day period following the index date; ARB use was not associated with an increased risk, but ACEI use was.

The sensitivity analyses involving different ways of adjusting for severity of hypertension (changing the exposure window from 90 to either 60 or 180 days prior to the index date, or excluding patients with a past history of congestive heart failure, diabetes and renal failure) all produced similar results.

Discussion

In response to concerns regarding the risk of sepsis arising from safety data from randomized controlled studies, in this study, the use of ARBs, including telmisartan, was not associated with an increased risk of sepsis or sepsis-associated mortality or renal failure in the 30 days following the onset of the sepsis episode, when compared with the other common classes of antihypertensive agents. However, the risk of sepsis associated with ACEI use was higher than with these common antihypertensive agents. In comparison to hypertensive patients who had not been prescribed antihypertensive agents, the risk of sepsis was

Table 4

Crude and adjusted odds ratios of sepsis-related renal failure associated with current use† of ARBs and ACEIs relative to current use† of beta-blockers, CCBs or diuretics (model 1) and to no antihypertensive drug use (model 2)

	Cases	Controls	Crude Odds ratio	Adjusted* Odds ratio	Adjusted* 95% CI
Number of subjects	346	3460			
Model 1: comparison with other antihypertensive drugs					
Current beta-blockers, CCB or diuretic use (%)	28.0	36.0	1.00	1.00	Reference
Current ARB use only (%)	3.8	4.3	1.15	0.89	0.46–1.71
Current ACEI use only (%)	20.8	11.9	2.27	1.75	1.22–2.52
Model 2: comparison with non-users of antihypertensive drugs					
No antihypertensive drug use in past year (%)	11.0	12.5	1.00	1.00	Reference
Current ARB use only (%)	3.8	4.3	1.02	0.85	0.42–1.73
Current ACEI use only (%)	20.8	11.9	2.01	1.67	1.06–2.63
Current beta-blockers, CCB or diuretic use (%)	28.0	36.0	0.89	0.96	0.62–1.47

Abbreviations are as follows: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval. *Adjusted for all covariates in Table 1. †Current use refers to a prescription within 90 days prior to the index date.

lower with current use of most classes of antihypertensive agents, but not with ACEI use.

Animal data suggest that chronic arterial hypertension may be associated with decreased mortality from sepsis, but this has never been examined in humans [24, 25]. However, as hypertension is often associated with older age and more co-morbid illnesses, particularly cardiac disease, patients with hypertension may, in fact, appear to have worse outcomes in observational studies. Moreover, the role of antihypertensive medications is unclear. Given that their mechanism of action involves vasodilatation or blocking physiological cardiovascular responses that are important in the maintenance of an adequate blood pressure, use of antihypertensives could worsen outcomes if they give rise to more severe and sustained hypotensive episodes during sepsis.

Agents that inhibit the synthesis of angiotensin II (ACEIs) or block its effects (ARBs) lower blood pressure by preventing vasoconstriction, as well as by preventing angiotensin II-dependent and aldosterone-dependent sodium reabsorption in the kidney. Interestingly, ACEIs have been associated with an increased risk of vasodilatory shock in some patient populations, such as postcoronary artery bypass and in certain patients during dialysis [26–28]. but this has not been described with ARBs. It is unclear why the risk appeared to be increased with ACEI use and not ARBs. One possible explanation for the discrepant findings among users of ACEIs and ARBs may be the additional bradykinin-related properties of ACEIs. Specifically, ACEIs inhibit the degradation of bradykinin, which has vasodilatory properties. Thus, the combined effect of increased bradykinin and decreased angiotensin II leads to a more exaggerated vasodilatory response with ACEIs than that seen with ARBs. Alternatively, it is possible that ACEI use is a marker of a patient population with greater cardiac comorbidity than the group of patients using other antihypertensive agents. While adjusting for ischaemic heart disease and congestive heart failure makes this less likely, we cannot exclude the possibility of residual confounding. The protective effect of some of the classes of drugs compared with untreated hypertension could be related to a 'healthy user' or 'healthy adherer effect', with ARB users having the lowest rate of discontinuation of their drug therapy [29–31]. Angiotensin-converting enzyme inhibitors were cheaper over most of this period, so ARBs may have been preferentially prescribed to younger patients with fewer comorbidities and higher social class. Some studies reported on the relationship between antihypertensive drugs and sepsis. In the POISE randomized trial, which compared the effect of the β-blocker metoprolol perioperatively with placebo in patients undergoing noncardiac surgery, death from sepsis or infection was significantly more common in patients who received metoprolol [4]. We, however, found that β-blockers (grouped with diuretics and CCBs) were not associated with such an increased risk of death from sepsis. Whether the presence of hypertension in our population plays any role in this difference in results is not known. Two observational studies assessed patients admitted for sepsis to determine whether medications taken before admission affected the prognosis of sepsis, particularly focusing on sepsis-associated mortality. These studies suggest a protective effect of statins and ARBs from worse outcomes of sepsis [9, 32].

The present study has strengths and limitations. The study population involved a large population-based cohort of over 550 000 patients observed over 10 years, a size and follow-up that enabled the identification of a large number of incident cases of sepsis and precise estimates of the risk for the drug classes under study. Despite this large size, the number of telmisartan users was relatively low to provide tight estimates of the risk. Nevertheless, the upper bound of 1.50 for the 95% confidence

interval of the rate ratio of sepsis with temisartan is in the same range as the 1.43 for all ARBs together, which provides some reassurance regarding the risk of telmisartan in particular. The subjects in our study were patients with diagnosed and/or treated hypertension, which was different from those studied in the large randomized trials that generated this hypothesis. Indeed, the subjects in our study were on average 10 years older than those in the PRoFESS and TRANSCEND trials, studies that were not limited to patients with hypertension. Selection bias was avoided by the completeness of the population-based cohort, which also provides generalizability. As the GPRD uses prospectively pre-recorded medication exposure information, recall bias is avoided. We restricted our study to the subcohort of the GPRD that could be linked with the HES hospitalization database, which would improve the validity of the sepsis outcome. This definition may, in fact, be more valid than that used in the randomized controlled trials where sepsis was not declared *a priori* in the protocol, but was rather one of several routinely reported adverse events. Our hospitalization-based case definition gave a calculated rate of sepsis of 6.9 per 10 000 per year in our cohort and 2.9 per 10 000 per year for sepsis-related death, which are in the same range as most other population-based rates. In the USA, the rate of sepsis from hospitalization records was estimated at 8.3 per 10 000 in 1979, but increased to 24.0 per 10 000 in 2000. However, the rate of sepsis leading to in-hospital death was 4.4 per 10 000 in 2000, similar to our estimate [15]. In Australia and New Zealand, the rate of sepsis was estimated at 7.7 per 10 000 population per year [33].

Other than for ACEIs, antihypertensive drug use appeared to decrease the risk of sepsis in hypertensive patients. In this case, non-use may, in fact, reflect a worsening clinical condition associated with a higher risk of sepsis, or the development of cardiac dysfunction in hypertensive patients, which can result in lower blood pressure and discontinuation of antihypertensive medications. Although we controlled for the presence of many co-morbid illnesses, residual confounding may be contributing to the association of ACEI with worse outcomes, because these drugs are also used in patients with worsening cardiac conditions.

In conclusion, ARBs as a class, including telmisartan, do not appear to be associated with an elevated risk of sepsis or sepsis-related acute kidney injury or death. The increase in the risk of sepsis observed with angiotensin-converting enzyme inhibitors merits further investigation.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: SS had support from Boehringer-Ingelheim for the submitted work; SD, SJN, AK and JB had no support from any organization for the submitted work; SD, SJN, AK and JB had no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; all authors had no other relationships or activities that could appear to have influenced the submitted work.

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